This Week in The Journal

● Cellular/Molecular

CaMKII and Angelman Mice

Derangements of Hippocampal Calcium/Calmodulin-Dependent Protein Kinase II in a Mouse Model for Angelman Mental Retardation Syndrome

Edwin J. Weeber, Yong-Hui Jiang, Ype Elgersma, Andrew W. Varga, Yarimar Carrasquillo, Sarah E. Brown, Jill M. Christian, Banefsheh Mirnikjoo, Alcino Silva, Arthur L. Beaudet, and J. David Sweatt

(see pages 2634–2644)

In this issue, Weeber et al. explore a mouse model of an uncommon neurological disorder and find unexpected perturbations in signaling associated with hippocampal long-term potentiation (LTP). Angelman Syndrome (AS) is characterized by mental retardation, ataxic gait, seizures, and an unusual affect. The disease most commonly results from deletion in the 15q11–13 region of the maternal chromosome. The responsible gene is *Ube3a*, which encodes E6-AP ubiquitin ligase, a protein-degrading enzyme. Because of genetic imprinting, E6-AP function is disrupted specifically in the hippocampus and in cerebellar Purkinje cells of affected individuals. AS mice with a null mutation in the maternal copy of the *Ube3a* gene also have ataxia, seizures, hippocampal learning defects, and region-specific paternal silencing of *Ube3a*. Deficits in LTP occur in these mice, but the link to E6-AP has been obscure. In the current work, the authors narrowed in on calcium/calmodulin-dependent protein kinase II (CaMKII). In AS mice, CaMKII showed increased autophosphorylation and reduced activity and was translocated away from the postsynaptic density. The changes in CaMKII appear to result from a dramatic reduction in the activity of protein phosphatase 1 (PP1)/PP2A. So what is the link to E6-AP? The authors suggest that p53 (which is targeted by E6-AP and accumulates in neurons of the AS mouse) may alter association of PP1 with a shared binding protein (p53BP2), and thus cause decreased phosphatase activity. These results provide a potential link between a learning deficit and loss of hippocampal LTP and also illustrate the complexities between gene defects and neurological phenotypes.

▲ Development/Plasticity/Repair

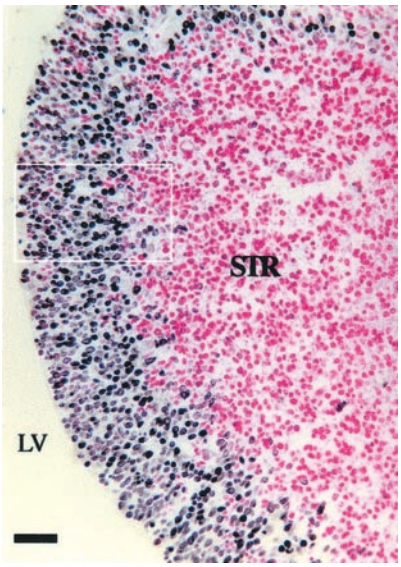
An Action of Dopamine Early in Development

Dopamine Modulates Cell Cycle in the Lateral Ganglionic Eminence

Nobuyo Ohtani, Tomohide Goto, Christian Waeber, and Pradeep G. Bhide

(see pages 2840–2850)

Monoamines have been implicated in the regulation of neuronal growth and sensory map formation during development. Ohtani et al. report an additional developmental role for these neuromodulators in the dopamine-rich neostriatum. They provide evidence of opposing actions of D1 and D2 dopamine receptor activation on the kinetics of neurogenesis in the lateral ganglionic eminence, the forerunner of many basal ganglia neurons. In explants, D1 activation selectively reduced entry of ventricular zone progenitors into S-phase, whereas D2 activation specifically promoted progenitor cell entry into S-phase in the subventricular zone. Consistent with the *in vitro* data, *in vivo* antagonism of D1 signaling resulted in a marked increase in bromodeoxyuridine (BUdR) labeling of CNS progenitor cells in the lateral ganglionic eminence. The authors suggest that the disruption of dopamine signaling *in utero*, for example by exposure to drugs of abuse during the first trimester of pregnancy, may have implications in altering the timing of neuron production and perhaps even the quantitative organization of neostriatal neurons as well as GABAergic interneurons that originate in the ganglionic eminence before migrating to other brain regions.



Section of an embryonic day 13 explant of the lateral geniculate eminence cultured for 12 hr. BUdR-labeled cells (*blue/black*) are prominent along the lateral ventricular surface (*LV*). This image is taken from Figure 2 of this article.

■ Behavioral/Systems/Cognitive

Serotonin and Prevention of Learned Helplessness

Freewheel Running Prevents Learned Helplessness/Behavioral Depression: Role of Dorsal Raphe Serotonergic Neurons

Benjamin N. Greenwood, Teresa E. Foley, Heidi E. W. Day, Jay Campisi, Sayamwong H. Hammack, Serge Campeau, Steven F. Maier, and Monika Fleshner

(see pages 2889–2898)

Although psychologists and runners alike have long known that consistent physical exercise can lower stress and help to fight off depression, an article by Greenwood et al. uncovers some clues as to how this occurs. Serotonergic neurons in the dorsal raphe nucleus (DRN) are thought to be key to learned helplessness, a behavioral measure of depression in animals exposed to uncontrollable stress. When serotonin (5-HT) floods the DRN during such a stressful episode, it is thought that inhibitory 5-HT type 1A (5-HT1A) autoreceptors are downregulated, leading to sensitization of the DRN neurons. This in turn may lead to hyperactivity of these serotonergic neurons that project to areas involved in the learned response to stress. The authors indeed found that rats that engaged in freewheel running for 6 weeks had decreased learned helplessness, attenuated stress-induced activity of DRN 5-HT neurons, and increased 5-HT1A receptor mRNA in the DRN, relative to their lazier counterparts. Interestingly, the exercising rats used a running wheel voluntarily when given access to it. Perhaps this report provides yet another reason for the more sedentary among us to make the same choice.